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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

DETAILED ACTION

In a telephone interview with Ms. Cathleen Rocco on May 22, 2002 it was brought to the examiner's attention that the Office action mailed April 5, 2002 contains discrepancies between the text of the Brief and the references thereto in "Response to Arguments" section of the Office action on page 10.

Therefore, the Office action mailed on April 5, 2002 is hereby vacated and the response period begins on the mailing date of the instant Office action.

In view of the Appeal Brief filed on January 18, 2002 (deposited with the US Postal Service on November 26, 2001), PROSECUTION IS HEREBY REOPENED. New grounds of rejection are set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(a) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(b) request reinstatement of the appeal.

If reinstatement of the appeal is requested, such request must be accompanied by a supplemental appeal brief, but no new amendments, affidavits (37 CFR 1.130, 1.131 or 1.132) or other evidence are permitted. See 37 CFR 1.193(b)(2).

Claims 18-22 are pending.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 19, with dependent claims 18 and 20-22, is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 19 recites "a naturally-occurring human polynucleotide sequence variant encoding an amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:1", thus encompassing all allelic variants of SEQ ID NO:1. There is no limitation on the function of the encoded protein. Thus, the genus of polynucleotides of claim 19 encodes proteins having pyrophosphatase activity and many inactive variants thereof.

Allelic variants are alternate forms of a gene which have at least one mutation in the nucleotide sequence which may result in mRNAs (polypeptides) with altered function. With regard to a naturally-occurring human polynucleotide sequence variant, there is no description of any mutational site that exist in nature, and there is no description of how the structure of SEQ ID NO:2 relates to the structure of any allele

including strictly neutral alleles. The general knowledge in the art concerning alleles does not provide any indication of how the structure of one allele is representative of unknown alleles. The nature of alleles is that they are variant structures, and in the present state of the art the structure of one does not provide guidance to the structure of others. Thus the claimed genus is extremely variable with the potential to encode proteins with widely variant functions. The common attributes of the genus are not described. Therefore, one of skill in the art would not conclude that applicant was in possession of the claimed genus because a description of only one member of this genus is not representative of the variants of the genus and is insufficient to support the claims.

Claims 18 and 20-22 are drawn to a method of use of a diverse genus of a probe comprising 15, 30 or 60 nucleotides complementary to SEQ ID NO: 2 or a naturally-occurring human polynucleotide encoding an amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:1 (a polynucleotide of claim 19). "Complementary" as defined in the specification does not require for a probe to be a fragment of a polynucleotide of claim 19, i.e. to be fully, or 100%, complementary thereto (page 7, lines 2-10). This genus includes many structurally and functionally unrelated DNAs.

The specification does not disclose structural or physico-chemical or biological characteristics of a polynucleotide probe comprising 15, 30 or 60 nucleotides that are

complementary to a polynucleotide of claim 19. The specification does not teach correlation between the structure and the function common to all members of the genus. Therefore, based on the instant disclosure, in view of the level of knowledge and skill in the art, one skilled in the art would not recognize from the disclosure that the applicant was in possession of the genus of a polynucleotide probe comprising 15, 30 or 60 nucleotides that are complementary to a polynucleotide of claim 19. Therefore, a naturally-occurring human DNA encoding a polypeptide comprising a sequence having 90% identity to SEQ ID NO:1 having no pyrophosphatase function and a method of use of a polynucleotide probe comprising 15, 30 or 60 nucleotides that are complementary to a polynucleotide of claim 19 lack sufficient written description needed to practice the invention of claims 18 and 20-22.

Claims 18 and 20-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of use of a fragment of SEQ ID NO:2 or a fragment of a DNA encoding an amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:1, said fragment consisting of at least 15, 30 or 60 nucleotides, does not reasonably provide enablement for a method of use of a polynucleotide probe comprising 15, 30 or 60 nucleotides that are complementary to a polynucleotide of claim 19. The specification does not enable any person skilled in

the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be in In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7)considered in determining whether undue experimentation is required, are summarized the predictability or unpredictability of the art, and (8) the breadth of the claims.

The specification does not support the broad scope of the claim which encompass all modifications and fragments of any sequence that comprises a fragment of SEQ ID NO:2 because the specification does **not** establish: (a) regions of the protein structure which may be modified without effecting the specific requisite activity of the polypeptide encoded by a DNA of the instant invention; (B) the general tolerance of said polypeptide to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement.

The state of the art does not allow the predictability of the properties based on the structure. The properties of a polypeptide of an unknown length and structure are unpredictable based on a fragment. Therefore, one skilled in the art would require guidance as to how to use a probe comprising 15, 30 or 60 nucleotides complementary to SEQ ID NO:2 or a sequence encoding an amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:1 wherein said probe is not a fragment of said sequences in a manner reasonably correlated with the scope of the claims. One skilled in the art would require further guidance as to how to use a naturally-occurring human polynucleotide encoding a polypeptide comprising a sequence having 90% identity to SEQ ID NO:1 having no pyrophosphatase function. Without such guidance, the experimentation left to those skilled in the art is undue.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 18 and 20-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 20, with dependent claims 21, 22 and 18, recites a probe having a sequence that is "complementary" that specifically hybridizes to a polynucleotide of claim 19. The term "complementary" is defined by non-limiting examples (page 7, lines 2-10). Absent specific definitions of the structure of a probe and/or specific hybridization conditions, it is impossible to know which structures are defined as a probe rendering the metes and bounds of the claim unascertainable.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 18 and 20-22 are rejected under 35 U.S.C. 102(b) as being anticipated by Yang et al.

Yang et al. (form PTO-1449, reference 2) teach cDNA encoding bovine pyrophosphatase. This sequence is more than 90% identical to SEQ ID NO:2 and comprises 15, 30 and 60 contiguous nucleotides thereof. Yang et al. teach a method of

detecting a target polynucleotide in a sample comprising polynucleotides from human retinas (page 24646, left-hand column, and Fig.8) and PCR amplification of a target polynucleotide (page 24642, 2nd column). SEQ ID NO: 2 or a naturally-occurring human polynucleotide encoding an amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:1 will be detected by the method taught by Yang et al. Therefore, the method of Yang et al. anticipates claims 18 and 20-22.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 18 and 20-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yang et al .

The teachings of Yang et al. are outlined above.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use a polynucleotide of Yang et al. to detect homologous sequences in a sample. A polynucleotide of claim 19 will be detected in a sample comprising polynucleotides prepared from a human tissue. It would have been further

obvious to one of ordinary skill in the art at the time the invention was made to amplify the target polynucleotide by PCR as it is routinely performed in the art. One skilled in the art would have been motivated to screen various human libraries for human orthologs of the bovine sequence in view of the importance of the pyrophosphatase in animals. One skilled in the art would have a high expectation of success because Yang et al. have actually shown the presence of a human ortholog in a sample from retinas.

Response to Arguments

Applicant's arguments filed January 18, 2002 have been fully considered but they are not persuasive.

With regard to a polynucleotide of claim 19 (SEQ ID NO: 2 or a naturally-occurring human polynucleotide encoding an amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:1) Applicants argue that "given the genetic code and SEQ ID NO: 1, all possible polynucleotide sequences are therefore described" (Brief, page 5). This is not persuasive because a polynucleotide encoding a disclosed SEQ ID NO:1 is not rejected. The rejection is made over a naturally-occurring human polynucleotide encoding any amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:1. None of said 90% identical sequences is disclosed.

Applicants continue "the specification also describes ... how to use BLAST to determine whether a given sequence falls within the "at least 90% polypeptide sequence identity" scope" (Brief, page 5, penultimate paragraph). These arguments are disagreed with because the issue of "determination of a percent of sequence identity" is an enablement matter and is different from the written description. While the species in question can be identified they are not described in a sufficient manner in the specification.

Applicants further argue that the current claims are fundamentally different from the types of claims the court has found to lack sufficient written description as the current claims recite the genus of polypeptides claimed in strictly structural terms while the claims found to lack written description in cases such as *Fiers v. Revel* (25 USPQ2d 1601) and *University of California v. Eli Lilly and Co.* (43 USPQ2d 1398) defined the claimed genus in strictly functional terms (Brief, pages 6-12). While it acknowledged that the current claims differ from those held by the court to lack sufficient written description, as discussed in the written description guidelines the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a

combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. A representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. Satisfactory disclosure of a representative number depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. For inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus. In the instant case the claimed genera of Claims 19 and 18, 20-22 includes species which are widely variant in function. Naturally occurring amino acid sequences having at least 90% identity to SEQ ID NO:1, includes allelic variants of SEQ ID NO:1 and all other loci which encode proteins having 90% identity to SEQ ID NO:1. Allelic variants encompass polypeptides **whose function may or may not be altered**. Claims 18 and 20-22 are drawn to a method of use of a diverse genus of a probe comprising 15, 30 or 60 nucleotides complementary to SEQ ID NO: 2 or a naturally-occurring human polynucleotide encoding an amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:1 (a polynucleotide of claim 19). This genus includes many structurally and functionally unrelated DNAs. The

genus of a probe comprising 15, 30 or 60 nucleotides complementary to a polynucleotide of claim 19 is even more structurally and functionally diverse as it encompasses polynucleotides encoding polypeptides with pyrophosphatase activity, those which lack such activity but are capable of hybridizing at unspecified conditions to a polynucleotide of claim 19 as well as an enormous number of polynucleotides encoding polypeptides with neither of these functions, but possibly other undisclosed functions. As such, neither the description of the structure and function of SEQ ID NO:1 nor the disclosure solely structural features present in all members of the genus is sufficient to be representative of the attributes and features of the entire genus. Applicant should note that the claims of the '740 patent in the *Lilly* case are limited by **both** structural limitations (the recited generic formula) and functional limitations (coding for human preproinsulin) and thus puts the artisan in possession of the attributes and features of all members of the claimed genus.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth Slobodyansky whose telephone number is (703) 306-3222. The examiner can normally be reached Monday through Friday from 9:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX phone number for Technology Center 1600 is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Center receptionist whose telephone number is (703) 308-0196.

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